similarity to SEQ ID NO:3 or hybridizes under low stringency conditions to a reverse complement of the nucleotide sequence of SEQ ID NO:3.

50. The nucleic acid of ~~Claim 43~~ Any one of Claims 44, 45 or 46 wherein said polypeptide has at least one of the following properties:

(i) an ability to induce vascular endothelial cells;

(ii) an ability to interact with *flt-1/flk-1* family of receptors; or

(iii) an ability to induce cell migration, cell survival or an increase in intracellular levels of alkaline phosphatase.

REMARKS

In the Office Action dated January 5, 1999, Claims 26-33 have been rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. Claims 26-33 and 35-36 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. Claims 26-33 and 35-36 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claims 26-28, 30-31 and 35-36 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tischer, et al. U.S. Patent No. 5,194,596 (hereinafter "Tischer, et al."). Claims 26-33 and 35-36 have been rejected under 35 U.S.C. §102(e) as allegedly anticipated by Eriksson, et al. U.S. Patent No. 5,607,918 (hereinafter "Eriksson, et

al."). The specification has been objected to in view of several alleged informalities.

In response to the above rejections, applicants have amended the claims, which when considered with accompanying comments is deemed to place the present application in condition for allowance.

The Examiner has objected to the specification, alleging that the title is not descriptive. Applicants have amended the title to reflect the invention to which the claims are directed. The Examiner has further objected to the figure legends in the Brief Description of Drawings at Page 10. Applicants have amended the brief description of Figures 8A and 8B to comport with the figure labeling requirements pursuant to 37 C.F.R. §1.84(u)(1). The Examiner has also alleged that the claims do not comply with 37 C.F.R. §1.821(d) which requires reference to a particular sequence identifier in the specification and claims wherever a reference is made to a sequence. Specifically, Claim 33 refers to a sequence as set forth in Figure 9. Applicants have amended Claim 33 by providing reference to SEQ ID NO:16 therein. Accordingly, the Examiner's objections have been overcome and withdrawal thereof is respectfully requested.

Claims 26-33 have been rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. The Examiner specifically alleges that the claims fail to include

limitations which "would distinguish the nucleic acids from ones which occur in nature." In response, applicants have amended the claims to recite "isolated" nucleic acid molecules. Accordingly, the rejection of Claims 26-33 under 35 U.S.C. §101 is overcome and withdrawal thereof is respectfully requested.

Claims 26-33 and 35-36 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. Specifically, Claims 26-28 have been rejected based on the recitation "proteinaceous molecule" which the Examiner alleges "does not convey the concept of a protein or polypeptide." In an effort to further favorable prosecution on the merits, the recitation "proteinaceous molecule" has been deleted in favor of claims which recite "polypeptides" in accordance with the Examiner's recommendation.

The Examiner has also rejected Claims 26-33 and 35-36 under 35 U.S.C. §112, first paragraph. The Examiner alleges that the specification, "while being enabling for nucleic acid molecules encoding the naturally occurring VEGF molecules, does not provide enablement for nucleic acid molecules which encode polypeptides which have least 15% similarity to SEQ ID NO:2 while retaining the biological activity of the protein of SEQ ID NO:2." Applicants respectfully submit that the specification is directed to molecules which have VEGF-like properties. Applicants further submit that the specification is enabling for nucleic acid molecules which encode VEGF-like

molecules. In an effort to further favorable prosecution on the merits, Claims 26 and 27 have been canceled without prejudice. New Claim 43 has been added which recites an isolated nucleic acid encoding a polypeptide having at least about 90% similarly to SEQ ID NO:2. The Examiner's attention is respectfully directed to the specification at Page 4, lines 25-28 which provides support satisfying the requirements of 35 U.S.C. §112. No new matter has been added by the submission of Claim 43.

The Examiner has rejected Claim 36 under 35 U.S.C. §112, first paragraph, alleging that the specification, while enabling for a method of making a protein, does not provide enablement for methods which use nucleic acid molecules which hybridize to a reference sequence to make the protein. In response, Claim 36 has been canceled, without prejudice and Claim 49 has been added. Claim 49 recites a method of making a protein wherein the nucleic acid molecule comprises a sequence that encodes a polypeptide having at least about 70% similarity to SEQ ID NO:3 or hybridizes under low stringency conditions to a reverse complement of the nucleotide sequence of SEQ ID NO:3. Support for Claim 49 may be found throughout the specification and particularly at Page 7, lines 7-15, for example.

Furthermore, Applicants submit that standard methods are employed to produce recombinant molecules based on expression of referenced nucleotide sequences as well as

sequences which hybridize to the referenced nucleotide sequences in the present specification. Moreover, "low stringency" hybridization conditions are specifically defined in accordance with the present invention. The low stringency hybridization conditions of the present invention employ "4-6 X SSC/0.1-0.5% w/v SDS at 37-45°C for 2-3 hours." (See Page 7, line 10).

Accordingly, the rejection of Claims 26-33 and 35-36 under 35 U.S.C. §112, first paragraph, are overcome and withdrawal thereof is respectfully requested.

Claims 26-33 and 35-36 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claim 26 has been rejected based on the recitation "at least one property in common" with VEGF. As previously indicated, Claim 26 has been canceled without prejudice thereby rendering the Examiner's rejection moot; withdrawal thereof is respectfully requested.

Claims 26, 31-32 and 35-36 have been rejected based on the recitation of "percent similarity." The Examiner alleges that the "use of percent identity or similarity is indefinite without a recitation of an algorithm for calculated identity." Applicants respectfully direct the Examiner's attention to the specification at Page 15, lines 29-32 which provides the underlying algorithm utilized by the invention to provide amino acid and nucleotide homology alignment.

Specifically, the "BESTFIT" program (GCG, University of Wisconsin) was used to calculate percent similarity in accordance with the present invention.

Claims 29 and 33 have been rejected as allegedly indefinite based on the recitation "substantially as set forth." In an effort to further favorable prosecution on the merits, the recitation "substantially as set forth" has been deleted from the claims. Claims 30-31 have also been rejected as allegedly indefinite for depending from non-elected Claim 1. Claim 30 has been amended to reflect proper dependency and Claim 31 has been canceled without prejudice.

Claims 32 and 36 have been rejected as allegedly indefinite based on the recitation "capable of hybridizing under low stringency conditions." As indicated above, the present application provides adequate definition of stringency conditions satisfying the requirements of 35 U.S.C. §112 for the recitation "low stringency conditions", thereby rendering the Examiner's rejection moot.

Claim 33 has been rejected as allegedly indefinite because "it is not clear which human VEGF is intended." Applicants have amended Claim 33 to provide proper reference to SEQ ID NO:16 corresponding to the nucleotide and peptide sequences derived from murine VEGF cDNA clones.

Claim 36 has been rejected because it is allegedly "not clear what the constitution of the nucleotide sequence is

from the claim." Claim 36 has been canceled without prejudice. Claim 49 has been added which clarifies that the nucleic acid comprises SEQ ID NO:3 or has at least about 70% similarity to SEQ ID NO:3 or hybridizes under low stringency conditions to a reverse complement of the nucleotide sequence of SEQ ID NO:3 in accordance with the teachings of the present invention.

Accordingly, in view of the foregoing amendments rejection of Claims 26-33 and 35-36 under 35 U.S.C. §112, second paragraph are overcome and withdrawal thereof is respectfully requested.

Claims 26-28, 30-31 and 35-36 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tischer, et al. Tischer, et al. allegedly teach a nucleic acid molecule which encodes a VEGF protein which has approximately 85% similarity to SEQ ID NO:2. The Examiner further alleges that Tischer, et al. teach a nucleic acid molecule which has 68% similarity to SEQ ID NO:3. The present invention (as claimed) provides isolated nucleic acid molecules encoding or complementary to sequences encoding a polypeptide comprising amino acid sequence having at least <u>about 90%</u> similarity of SEQ ID NO:2. The present invention further provides isolated nucleic acid molecules comprising SEQ ID NO:3 or having at least about 70% similarity to SEQ ID NO:3. Tischer, et al. fail to teach the invention (as claimed) because the protein of Tischer, et al. has only about 85% similarity to SEQ ID NO:2

and the nucleic acid of Tischer, et al. has only about 68% similarity to SEQ ID NO:3.

Accordingly, the rejection of Claims 26-28, 30-31 and 35-36 under 35 U.S.C. §102(b) is overcome and withdrawal thereof is respectfully requested.

Claims 26-33 and 35-36 have been rejected under 35 U.S.C. §102(e) as allegedly anticipated by Eriksson, et al. The Examiner alleges that Eriksson, et al. teach a nucleic acid molecule which encodes a protein having the amino acid sequence of SEQ ID NO:6. The Examiner further alleges that SEQ ID NO:11 of Eriksson is the same as that of SEQ ID NO:6 of the instant application. The Examiner notes that Eriksson, et al. claim priority to U.S. Appln. Serial No. 08/397,651, which has a filing date of March 1, 1995 and "therefore constitutes prior art against the instant application."

Assuming pro arguendo, the relevance of the cited reference, Applicants respectfully submit that the Examiner has not established that Eriksson, et al. is in fact prior art to the present invention. Applicants note that Application Serial No. 08/469,427 was filed as a continuation-in-part of Application Serial No. 397,651 which was filed on March 1, 1995. The Examiner has not established on the record that the cited SEQ ID's of Eriksson, et al. are, in fact, entitled to the priority of 08/397,651 (i.e., March 1, 1995). Instead, Eriksson, et al. prima facie are entitled to a filing date of

June 6, 1995 which is after applicant's priority date of March 2, 1995. However, in an effort to further favorable prosecution on the merits, Claims 26, 29 and 31 have been canceled without prejudice.

The Examiner alleges that Claim 33 is drawn to the nucleotide sequence of Figure 9 (SEQ ID NO: 16) which encodes a protein having SEQ ID NO:17. The Examiner alleges that SEQ ID NO:17 is the same protein as taught by Eriksson in Figure 12 of SEQ ID NO:5. Applicants submit that the rejection of a claim under 35 U.S.C. §102(e) requires that the prior art reference disclose every element of the claim. It is axiomatic that there must be no differences between the subject matter of the claim and the disclosure of the prior art. The absence from the reference of any claimed element negates anticipation Kloster Speedsteel AB v. Crucible Inc. 793 F.2d 1565, 1571, 230 U.S.P.Q. 81, 84 (Fed. Cir. 1986). Claim 33 (as amended) recites a nucleotide sequence of Figure 4 (SEQ ID NO:16) which is not taught by Eriksson, et al. SEQ ID NO:16 contains 205 amino acids whereas the polypeptide of SEQ ID NO:5 of Eriksson is only 188 amino acids long. Accordingly, the rejection of Claims 26-33 and 35-36 under 35 U.S.C. §102(e), is overcome and withdrawal thereof is respectfully requested.

Applicants reserve the right to pursue the subject matter of the canceled claims in a continuing application.

Thus, in view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance, which action is respectfully requested.

Respectfully submitted,

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